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PHYSIOLOGICAL REVIEW

The reorganisation of memory during sleep

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SUMMARY

Sleep after learning promotes the quantitative strengthening of new memories. Less is known about the impact of sleep on the qualitative reorganisation of memory, which is the focus of this review. Studies have shown that, in the declarative system, sleep facilitates the abstraction of rules (schema formation), the integration of knowledge into existing schemas (schema integration) and creativity that requires the disbandment of existing patterns (schema disintegration). Schema formation and integration might primarily benefit from slow wave sleep, whereas the disintegration of a schema might be facilitated by rapid eye movement sleep. In the procedural system, sleep fosters the reorganisation of motor memory. The neural mechanisms of these processes remain to be determined. Notably, emotions have been shown to modulate the sleep-related reorganisation of memories. In the final section of this review, we propose that the sleep-related reorganisation of memories might be particularly relevant for mental disorders. Thus, sleep disruptions might contribute to disturbed memory reorganisation and to the development of mental disorders. Therefore, sleep-related interventions might modulate the reorganisation of memories and provide new inroads into treatment.

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Introduction

Learning, memory and the neural plasticity underlying these processes are fundamental characteristics of animals and humans that allow for adaptation in changing environments. Research over the past years has shown that sleep after learning facilitates the *quantitative strengthening* of newly encoded and initially instable memory traces (for review, please refer to [1]). Quantitative strengthening refers to the veridical preservation of stored information and stabilises memories against disruptive interference and decay [2].

More recently, it has been proposed that sleep might also promote the *qualitative reorganisation* of memories; i.e., the emergence of new memory content that has not been directly learned. This reorganisation of memories during sleep will be the focus of the current review.

A comprehensive model of sleep and memory was recently proposed [3]. This model overarches the entire fate of a novel memory trace from selectivity in initial processing to its subsequent strengthening and further memory evolution; these processes may, at least partially, be interlinked and complementary. The present review elaborates on memory evolution in the form of qualitative changes in memory content rather than the earlier steps of initial processing or strengthening.

Specifically, we review and integrate the current literature related to the two major memory systems, the declarative and the procedural motor systems, from a behavioural perspective. Subsequently, we review the potential neural mechanisms underlying these systems and the modulation of memory reorganisation by emotions. In the final translational section, the potential implications of sleep-related memory reorganisation for the aetiology and treatment of mental disorders are discussed.

Memory reorganisation – the concept

Human memory is an adaptive system. We do not only consolidate experiences as literal records of the past, but we also transform those experiences into new representations that might substantially differ from what was originally encoded [4]. To the best of our knowledge, Sir Frederic Bartlett was the first to

Abbreviations: NREM sleep, non-rapid eye movement sleep; PTSD, post-traumatic stress disorder; REM sleep, rapid eye movement sleep; SWS, slow wave sleep.

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Glossary of terms

Memory reorganisation	changes in memory content that are reflected by qualitatively new memories that have not been directly learned
Memory strengthening	the veridical preservation of stored information
Schema	mental framework for the organisation and understanding of information that enables the extraction of rules or general concepts on the meta-level

systematically show that memory is constructive in nature [5]. In his famous experiments on repeated reproduction, participants were asked to learn and reproduce a North American folk tale called *The War of the Ghosts*. This tale contains a number of inconsistencies that are puzzling for participants with European socialisations. For example, the text 'One night, two young men from Egulac went down to the river to *hunt seals*, [...]' was frequently transformed and normalised to '[...] went down to the river to *go fishing*, [...]' in the participants' reconstructions. Bartlett's pioneering findings demonstrated that text reproductions are often inaccurate and primarily represent modified versions (i.e., reorganisations) of the original text in which unusual aspects are altered into more typical scenarios.

These findings led Bartlett to introduce the concept of *schema* as a framework for the organisation and understanding of information [5]. Specifically, schemas capture the ability to systematically organise a multitude of facts and experiences and to extract the general gist which enables the transfer of pre-existing knowledge to novel stimuli and situations. For example, the schema '*dog*' allows for differentiating this species from others, such as cats. Other examples of the constructive nature of memory include observations of erroneous autobiographical memories [6], inconsistencies in eyewitness testimonies [7], and memory distortions in patients with mental disorders [8].

In the following sections, we review and discuss the role of sleep in the reorganisation of memories. We focus on findings from human research and the behavioural perspective of reorganisation. Subsequently, we provide some thoughts on the potential neural mechanisms of this reorganisation. We first discuss memory reorganisation in the declarative system and then discuss reorganisation in the motor system. Studies that comprise both declarative and procedural components are arranged according to their main outcome parameter (Table 1).

Table 1
The reorganisation of memory in the declarative and motor memory system.

Declarative memory
Schema formation
Extraction of rules
Generalisation
Schema integration
Integration of recent and remote memories
Relational memory
False memory formation
Schema disintegration
Associative thinking
Creativity
Motor memory
Movement automatisation
Motor schema
Implicit extraction of rules
Generalisation

The reorganisation of declarative memory during sleep

Declarative memory refers to the memory of events and facts. Declarative memory is believed to emerge from synaptic long-term plasticity in a hippocampal–neocortical network [9]. Based on our integration of the literature, we propose a multi-process model comprising *schema formation*, *schema integration* and *schema disintegration* (Fig. 1). More specifically, *schema formation* arises from the extraction of rules. These rules can then be generalised to novel situations. *Schema integration* pertains to the integration of recent and remote memories, relational memory and the emergence of false memories. *Schema disintegration* describes the process of disbanding existing schemas to allow 'outside the box thinking' and creativity. These schema processes might be associated with distinct sleep characteristics; schema formation and integration might predominantly rely on slow wave sleep (SWS) during non-rapid eye movement (NREM) sleep, whereas schema disintegration might primarily relate to rapid eye movement (REM) sleep. Evidence for and the limitations of these concepts are discussed in the following sections.

Schema formation

Out of a multitude of single pieces of information, a novel schema may emerge. For example, children learn to identify a dog as a dog after having seen many different dogs. As a result, a novel level of information processing in form of the extraction of rules and generalisation might occur. This process has recently been referred to as multi-item generalisation, and sleep plays an important role in this process [3].

Extraction of rules

A pioneering demonstration of the impact of sleep on the extraction of rules was provided by Wagner and colleagues [10]. Using a declarative number reduction task with an embedded deterministic rule, the authors showed that the number of subjects who were able to extract the hidden rule doubled after a night of sleep compared to sleep deprivation or daytime wakefulness of equal duration. However, sleep was not necessary for all participants; some also extracted the rule without sleep, or even directly without the need for prolonged incubation.

The facilitation of rule-extraction during sleep has been replicated in other studies [11,12]. Pace-Schott and colleagues [11] replicated this facilitation using the Iowa Gambling Task, which contains complex probabilistic rules. In contrast to the study on deterministic rule learning by Wagner and colleagues [10] in which some of the participants also extracted the hidden rule without sleep, the participants in the study by Pace-Schott and colleagues benefited from the post-training interval only if that interval was spent sleeping. However, it remains unclear whether this effect is due to an active (i.e., sleep-specific brain activity) or passive (i.e., reduction of interference) effect of sleep. Indirect evidence for a sleep-specific effect has been provided by studies that have reported that rule-extraction is correlated with SWS [13–16] and increases in EEG activity in the 8–12 Hz frequency band [17]. Accordingly, Wilhelm and colleagues [16] showed that the benefit of sleep for explicit rule extraction is greater in children than in adults, and this effect may be a result from the greater amounts of SWS that occur during earlier periods of development.

Some studies have reported that the extraction of explicit rule-knowledge develops immediately after sleep [18,19]. Other studies have reported that sleep only has a priming effect on the capacity for rule-extraction; i.e., knowledge about the hidden rule is not immediately available after sleep but rather requires further

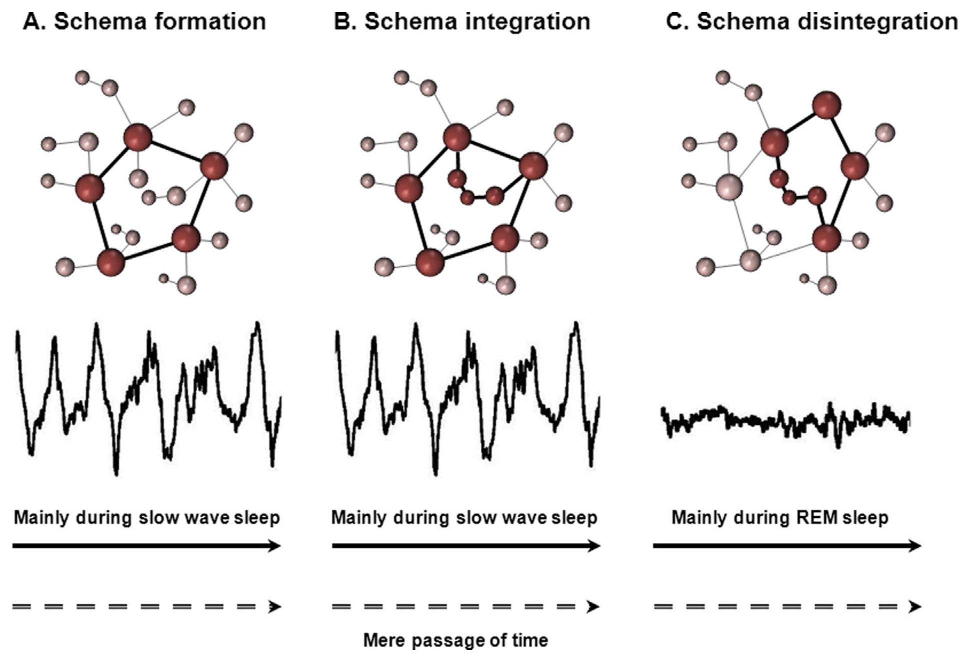

Fig. 1. Different forms of memory reorganisation in the context of schemas. Smaller dots represent less prominent nodes in a memory network, while thin lines represent their interrelations. Larger dots represent relevant components of a schema. Thicker lines symbolise the correlations between the central gist nodes. **A**. Schema formation. The general gist can be extracted from multiple experiences, which enables consequent generalisation to novel but similar situations. **B**. Schema integration. New memories can become incorporated into pre-existing schemas and memory networks and thus interrelate recent and remote memories. **C**. Schema disintegration. In the process of associative thinking and creativity, pre-existing schemas have to be disbanded to create a new schema. A and B seem to take place preferentially during slow wave sleep, whereas C seems to occur mainly during rapid eye movement sleep.

repetitions to emerge [10,11]. The explanation of these observations may be related to evidence that hints provided prior to sleep can serve as triggers for rule extraction via the tagging of relevant memory traces [20]. Djonlagic and colleagues [12] used a probabilistic memory task to demonstrate that the recall procedure is also a critical factor. In this study, for observational learning only, off-line memory enhancement was observed following a night of sleep, but no enhancement of feedback learning was observed.

Better determinations of the task-specific factors and settings (e.g., hints, rewards, and the levels of difficulty) and their interactions with sleep are required to further unravel the effect of sleep on the extraction of rules.

Generalisation

Another outcome of schema formation that arises from the abstraction of commonalities is the capability to confer past experiences onto novel situations; this ability is called generalisation [21].

The first study on sleep-related generalisation was conducted by Fenn and colleagues [22] who used an auditory spoken-language learning task. In this task, the ability to generalise is indexed by improved performance for novel, similar-sounding words that contain the same phonemes but different acoustic patterns. The authors demonstrated significant improvements in generalisation that immediately followed training and were stabilised by sleep but decreased across a 12 h retention interval without sleep. However, the ability to generalise completely recovered when the awake retention interval was followed by a night of sleep. These findings suggest that sleep not only stabilises but also restores the ability to generalise.

Beyond this restorative and stabilising effect, studies of infants suggest that sleep increases the ability to generalise and that naps are sufficient for this process [23,24]. In one such study, 15-mo old infants were able to generalise a grammatical pattern of a briefly presented artificial language to similar but unknown sentences after a nap but not after an equal period of wakefulness. This effect was measured 4 h after learning [24] and persisted over 24 h [23]. It remains unclear whether intense training or moderate training followed by sleep is more efficient.

Schema integration

Schema integration refers to the incorporation of initially distinct memories. Qualitatively new forms of memory, such as *integrational*, *relational* and *false* memories, can emerge through the mechanism of schema integration. Schema integration is important for learning and memory in a variety of domains; e.g., the acquisition of language. Schema integration is also important for the acquisition and understanding of complex material because new material can be more rapidly understood if a schema already exists [25]. In recent years, the evidence suggesting that sleep facilitates the process of schema integration has increased.

Integration of recent and remote memories

The human brain frequently integrates recent and remote memories [26]. Piaget has referred to the integration of new memories into pre-existing memory networks as *assimilation*. Additionally, pre-existing memory representations can be transformed by novel information in a process that is traditionally termed *accommodation* [27].

Memory assimilation. In humans, the assimilation of new memories into pre-existing networks has been examined using lexical competition [28]. In this paradigm, participants are asked to learn non-words along with similar-sounding familiar words (e.g., *cathedruke* as a lexical neighbour to *cathedral*). The integration of the newly constructed words into the mental lexicon is indexed by an inhibitory effect on reaction times for familiar words during auditory word recognition. Based on this paradigm, several studies have demonstrated that newly encoded words are better integrated into pre-

existing lexical stores after nocturnal sleep than after equal periods of wakefulness [29–31]. However, memory change in terms of lexical integration does not necessarily depend on sleep. For example, lexical integration can also occur within a single day without sleep if specific conditions are fulfilled; e.g., repeated exposure to related, remote memories [32]. However, complete lexical integration appears to be a process that occurs over several days [31].

An important study of rats has also provided evidence for the integration of new memories into pre-existing memories. This study demonstrated that newly paired flavour–place associations are encoded faster if a schema already exists [33,34].

In sum, sleep may facilitate memory assimilation, despite the fact that memory facilitation (e.g., lexical integration) can also occur without sleep. Perhaps, it is simply the interaction between sleep (and its different stages) and wakefulness (with repeated exposure) that provides the ideal conditions for memory assimilation. The extent to which these results can be extrapolated to the complex processes of everyday memory integration remains to be further elucidated.

Memory accommodation. Accommodation can take place when remote memories become unstable after reactivation, which makes them susceptible to the incorporation of new material [35]. According to the reconsolidation theory, the reactivation of a memory during wakefulness destabilises the trace and requires a process of reconsolidation to prevent that a memory deteriorates and/or is erased [36].

A seminal study by Hupbach and colleagues [37] confirmed that memory accommodation does not occur immediately but rather requires time and perhaps sleep to develop. In this study, participants learned a first list of objects on day one. On day two, they learned another list of objects; one group learned the second list in combination with a hint that reminded them of the first list, and another group did not receive this hint. The participants who received the hint incorrectly intermixed items from the second list when recalling the first list on day three but did not do so immediately after learning the second list on day two. This effect did not emerge prior to day three, including a retention interval with sleep. Whether it is sleep or the mere passage of time that promotes memory accommodation remains unclear.

Strikingly, reactivation does not always render a memory susceptible to the integration of new information. In contrast to wakefulness, SWS appears to stabilise memory traces in their original form when reactivated [38].

Furthermore, the direction of memory transformation is unclear. When do assimilation (i.e., a change in the newly acquired memory) and accommodation (i.e., changes in remote memories due to more recent memories) occur? Presumably, the order depends on additional factors, such as the context and the type of the presentation (e.g., single vs. repeated exposure). For example, the spatial context can serve as a schema in which new memories are integrated [39].

Future studies are needed to determine which stages of sleep foster the assimilation of new memories and which foster the accommodation of remote memories and the circumstances under which memory traces are simply consolidated in their original form. Through the processes of assimilation and accommodation, qualitatively new forms of memory can emerge. These new forms of memory and their interrelations with sleep are presented in the following two sections.

Relational memory

Relational memory is a specific form of schema integration. Relational memory refers to the capacity to form associations across events that did not exist before and to generate novel combinations of formerly distinct learned facts [21].

The first demonstration of the facilitation of relational memory by sleep was provided by Ellenbogen and colleagues. These authors used an inferential learning task with an embedded hierarchy [40]. In this task, participants were required to learn separate premise pairs that contained overlapping elements ($B > A$, $C > B$, $D > C$, where '>' stands for 'should be selected over'). The ability to combine the discrete elements in novel ways was neither present immediately after encoding nor after a 20 min interval but emerged 12 h later. Interestingly, the participants were significantly better able to make second order transitive inference judgements that required two logical operations (e.g., $A < D$) following sleep (compared to wakefulness). In contrast, no differences were observed for first order transitive inference judgements (e.g., $A < C$). Notably, even the second order transitive inference judgements could be executed without sleep; however, 25% fewer correct solutions were provided compared to the sleep condition.

Controlling for circadian factors and effects of sleep deprivation, Lau and colleagues [41] demonstrated a sleep-related facilitation of relational memory after a daytime nap. Again, a facilitation of relational memory also developed as a function of time without sleep, but this facilitation was attenuated compared to the sleep condition.

The results of both of these studies indicate that sleep has an enhancing effect on relational memory formation. To date, it remains unresolved whether this effect is due to the absence of interfering stimuli during sleep or sleep-specific neural activity patterns. However, the study by Lau and colleagues [41] is consistent with the concept that sleep has an active role. In this study, relational memory performance was selectively correlated with the duration of SWS during the nap. A variety of tasks have been investigated, and the sleep-related facilitation of relational memory appears to be at least partially independent of the material used.

False memory formation

Another, often unwanted, by-product in the process of memory change is the evolution of false memories. Here, people recollect events that never actually happened [42]. The most widely used paradigm for the elicitation of false memories that also has been used in sleep studies is the Deese–Roediger–McDermott task [43]. In this task, participants are instructed to learn word lists that are composed of semantically associated words but do not include the most strongly associated gist word, which is the theme of the list (e.g., *bed*, *rest*, *awake*, *tired* and *dream*, but not *sleep*). In this example, the word *sleep* would have a high probability of subsequently being incorrectly retrieved or recognised as a critical lure.

For both free recall and recognition studies using the Deese–Roediger–McDermott task, various findings have been reported that are challenging to integrate due to the use of different experimental designs. For free recall, a preferential production of false memories following sleep [44,45] and sleep deprivation [45] has been observed in comparison to daytime wakefulness. Whereas these results for free recall after sleep and sleep deprivation could be complementary (please refer to the potential explanations below), the findings for the recognition paradigms are contradictory. Indeed, one study found an enhanced recognition of false memories following sleep as compared to sleep deprivation [46]; however, two other studies reported a reduced recognition of false memories after sleep as compared to daytime [47] or nighttime wakefulness [48]. In the latter study, the enhanced recognition of false memories after sleep deprivation could be annihilated by the administration of the adenosine receptor antagonist caffeine, which implicates adenosinergic mechanisms in the recognition of false memories after sleep deprivation.

Using Deese–Roediger–McDermott lists with emotional content, McKeon and colleagues showed an increased recall of false emotional and non-emotional memories following sleep [49]; however, recall of veridical items following sleep was only greater for non-emotional words. These findings suggest specific mechanisms for emotional memory that will be discussed in more detail later in this review.

There are several potential explanations for the diverging results on false memory formation. First, it has been proposed that recognition may be based on source monitoring processes that are disturbed following sleep deprivation [48]. Thus, upcoming false memories might emerge on the foundation of representations that are automatically associated as part of the participant's schema into which the material was assimilated. Another hypothesis suggests that the abstraction of a general gist (schema formation), together with the fading of specific details, results in the evolution of false memories. This process, however, should not solely result in increases in false memories but should also result in decreases in veridical item memories; thus, the empirical evidence does not support the abstraction-of-gist hypothesis [44,47]. A third possibility that corroborates false memory formation following sleep assumes that false memories result from spreading activation. According to this concept, activations from the list items lead to the activation of the most strongly associated word [50]. Here, sleep might be especially favourable because no novel stimuli disrupt this process. Unfortunately, none of these hypotheses have been consistently supported by empirical evidence. To date, the processes underlying the production of false memories are not clear; do false memories emerge on the ground of reorganisation during sleep (off-line), or are they produced anew during recall or recognition (online)? Furthermore, little is known about the sleep-specific neural mechanisms that may provide useful insight into the formation of false memories.

Schema disintegration

Beyond the formation and integration of schemas, the highest level of memory change requires the disintegration of existing schemas as a prerequisite for the creative use of memory representations on a meta-level in the forms of associative thinking and creativity.

Associative thinking

Qualitatively new forms of memory also emerge in the process of associative thinking. Associative thinking refers to mental activity in which pieces of information are combined in novel ways and is often defined as 'the forming of associative elements into new combinations which either meet specified requirements or are in some way useful' [51]. Studies on associative thinking have focused on performance after experimental awakenings during different sleep stages. This approach is based on the idea that stage-specific brain activity patterns persist for a certain period of time after awakening. Nearly all of these studies have demonstrated that associative thinking benefits from being awakened from REM sleep. For example, performance in solving anagram word puzzles is enhanced after being awakened from REM sleep [52]. Furthermore, awakenings from REM sleep have been shown to benefit the learning of weak (e.g., *thief – wrong*) but not strong primes (e.g., *hot – cold*) compared to awakenings from NREM sleep or wakeful performance [53].

Creativity

Memory reorganisation also occurs in the form of creativity. Recent studies have used the compound remote associates task [54]. In this task, participants are required to find a fourth word that produces a meaning in combination with three unrelated words (e.g., *dream – break – light*, with the solution of *day*: *daydream*, *daybreak*, *daylight*). Participants who napped solved the items for which the solutions were primed more frequently than did participants who did not nap [55]. Here again, the effect did not emerge after sleep in general; rather this effect was specific to REM sleep. A sleep-specific advantage has also been reported in the absence of precedent priming, but this effect only occurred for the difficult items [56].

Another interesting study indicated that the reactivation of memory traces during sleep might promote creative solutions [57]. After conditioning a creative problem with an odour, participants who were exposed to the odour during sleep were better at solving the task than those who were not exposed to the odour. However, because this study did not include an awake control group, it is not clear whether the authors observed a sleep-specific effect. Together, the current but limited body of evidence suggests that REM sleep specifically fosters creativity.

The reorganisation of motor memory during sleep

The motor memory system entails a heterogeneous collection of implicit abilities and skills [58]. In contrast to the declarative system, the motor memory system is largely independent of the hippocampus and is primarily mediated by the basal ganglia, cerebellum and other brain structures [59]. Motor memory is commonly thought to comprise a process of stabilisation [60] and a gain in performance [61]. According to a widely accepted concept, in addition to mere strengthening, motor memory also includes a process of reorganisation but does not involve isolated memory traces; rather, patterns of motions are developed and strengthened.

Effects of sleep on different forms of motor memory changes have been observed [62], and performance gains primarily develop during offline-periods of sleep [60,63]. Notably, it is particularly difficult to differentiate strengthening from qualitative changes in the motor system because these processes appear to be intrinsically intertwined. In the following paragraphs, the steps involved in the development of a motor schema will be described; these steps begin with the relatively simple automatisation of single movements and proceed to the extraction of higher-level rules and complex processes of generalisation (see also Table 1).

Movement automatisation

During the initial training of a motor skill, learning is reflected in increases in the automatisation of distinct movements. Formerly distinct motor representations become integrated, and new relations may emerge [64]. Critically, recent studies have highlighted the importance of pre-sleep performance levels for the subsequent benefits acquired during sleep [65,66].

A common paradigm for the investigation of motor memory is the finger sequence tapping task [67]. In this task, participants type a sequence that is presented on a computer screen as fast and accurately as possible. Kuriyama and colleagues [68] demonstrated a form of sleep-associated memory reorganisation on the behavioural level. Immediately after learning a sequence, the participants' reproductions were disrupted by brief pauses. Fewer pauses occurred after a period of sleep than after a period of wakefulness, which reflects the emergence of new relations and the increased cohesion of the material. Similarly, this process of cohesion has been reported in other studies employing this and other motor tasks [60,69–71]. Notably, the effect of sleep on the cohesion of a finger skill is dependent on the participants' awareness during the training session [72]. Thus, sleep improves performance when the

motor skill has been explicitly acquired. In contrast, no benefit of sleep has been observed after implicit learning.

Motor schema

After extended training, a complex schema may emerge on the foundation of a multitude of automatised simple movements [73]. In contrast to declarative memory, the construct of motor skills consists of two parts, a goal-based component and a movement-based component [74]. Several studies have suggested that sleep predominantly fosters the development of the goal-based component, which represents the abstraction of a general procedural schema or pattern. In contrast, the movement-based component represents the consolidation of task-specific movements and appears to occur mainly during wakefulness [75–77].

Robertson proposed that short bouts of practice might favour the consolidation of the goal-based component during sleep and that prolonged training periods might promote the movement-based component, and thus the benefits of consolidation might develop predominantly during wakefulness [74].

Implicit extraction of rules

Rules can be extracted based on a schema. To date, the findings regarding rule-extraction from motor memories during sleep are inconsistent. The serial reaction time task has frequently been used in this domain and entails both a declarative and a motor component [78,79]. This task requires responses as fast and accurate as possible to a cue that is presented at different horizontally arranged positions on a computer screen. Unknown to the participants, the positions of the cue are determined by a sequence grammar. Implicit (reflected in reduced reaction times compared to a random sequence) and explicit learning (assessed by letting the participants explicitly generate the sequence structure) can be determined.

While some studies have observed sleep-related effects on implicit and explicit rule-extraction in adults using the serial reaction time task [19,20,80], other studies using the same or similar tasks have not shown any sleep-related effects [81,82]. In 7- to 11-y-old children, the opposite effects of implicit task knowledge after training have been described [80]. In addition to the differences related to sleep, these contradictory results might result from varying levels of task difficulty [66,80] or interference effects that occur between explicit and implicit learning [74].

Generalisation

Generalisation in the motor system occurs when a motor skill that has been learned in one context is transferred to another context [83]. Here, sleep has been reported to produce an advantage in the transfer of finger tapping performance from one hand to the other in the finger sequence tapping task [84] and in the serial reaction time task [76]. Similarly, participants are able to execute finger tapping sequences learned by observation but only when the learning session is followed immediately by sleep [85]. Once sleep has consolidated the skill memory, the ability to transfer and generalise a finger sequence to the opposite hand seems to be resistant to degradation, and performance is independent of whether the skill is tested on the next morning or the next evening [84]. This effect is comparable to the declarative generalisation effects [22]. No advantages for mirror sequences in which the finger movements remain the same (but made with the other hand, which represents the movement-based component) have been observed after sleep [84].

Deregnaucourt and colleagues [86] investigated the generalisation of procedural memories in animals and showed that song-structures that birds listen to in the evening are generalised to the own songs in the morning following sleep but not after wakefulness.

The greatest benefit to motor-memory generalisation has been observed when training is immediately followed by sleep [85,87,88].

Proposed neural mechanisms of memory reorganisation

Three major hypotheses related to the reorganisation of memories on the neural level have been proposed: the *complementary learning systems model* [89], the *synaptic homeostasis hypothesis* [90], and the *spreading activation theory* [50]. In the following, we briefly summarise these hypotheses and then provide some thoughts about their potential integration into the current framework of memory reorganisation.

The complementary learning systems model

The complementary learning systems model proposes two memory stores that are particularly relevant to declarative memory: the hippocampus and the neocortex [89,91]. According to this model, new memories are initially stored in the hippocampus. The hippocampus then acts as an internal ‘trainer’ and redistributes new memories to the neocortex for long-term storage [92]. Subsequently, connections within the neocortex are strengthened and become increasingly independent of the hippocampus [93].

It has been proposed that the readout of the hippocampus might preferentially take place during sleep [94], particularly during SWS [38]. Specifically, the combination of cortical slow oscillations (<1 Hz), thalamo-cortical activity in the electroencephalogram (EEG) delta range (1–4 Hz) and sleep spindles is thought to foster the hippocampal–neocortical dialogue [95]. For further discussion of the potential neural mechanisms please refer to the review by Diekelmann and Born [96].

In addition to the quantitative strengthening of memories, the hippocampal–neocortical dialogue may also result in qualitative changes at the behavioural level [97]. For example, correlations between relational memory and SWS [41] and between memory integration and sleep spindle activity [29] have been observed. On the level of neural systems, an functional magnetic resonance imaging (fMRI) study of the development of statistical knowledge suggested that a hippocampal–neocortical transfer occurs during the period of sleep and that weaker parahippocampal responses occur following sleep than following wakefulness [98]. Although the complementary systems model has mostly been studied in terms of declarative memory, this model may also apply to memory formation in other systems and has even been used to explain immunological memory formation [99].

The synaptic homeostasis hypothesis

Another important model is the synaptic homeostasis hypothesis [100]. This hypothesis proposes a global downscaling of synaptic strength during SWS that improves the signal-to-noise ratio. It also explains some findings related to the extraction of rules [15,18]. Specifically, if rule-extraction relies on the formation of overlapping elements, these elements might be the elements that are most strongly encoded and most likely to survive synaptic downscaling. However, the hypothesis does not appear to explain some processes of qualitative change, such as higher order relational memory [40] and associative thinking and creativity [55,56]. Here, qualitative changes in memory result from the enrichment of formerly encoded material by the development of new relations, while the downscaling of formerly active synapses can primarily explain the extraction of commonalities from overlapping elements.

The spreading activation theory

Other forms of memory reorganisation are not related to the processing of newly acquired memories but are related to novel combinations of pre-existing memories. The spreading activation theory may provide a theoretical framework for these forms of memory. This hypothesis proposes that neural activation can spread between previously encoded memory representations. Consequently, similar or associated memory traces might be linked together to form a novel network [50], and changes in synaptic connectivity in localised neuronal circuits may occur [92]. This process might preferentially take place during sleep due to the maximal reduction in external interference during this period and may be particularly related to the highly associative state of REM-sleep [96,101]. In support of these notions, nearly all studies of sleep-related associative thinking and creativity have shown that these processes are associated with REM sleep [52,53,55,56,102]. Moreover, studies of the content of dreams are consistent with the spreading activation theory in that they suggest that formerly processed material is reactivated during sleep [103,104]. These findings support the notion that dreams and processes of memory reorganisation are linked.

The neurophysiology of REM sleep might provide particularly favourable conditions for spreading activation. During REM sleep, the level of cholinergic neurotransmission is high and aminergic neurotransmission tone is low; this pattern of neurotransmitter levels reduces the hippocampo-neocortical readout and facilitates spreading activation within the neocortex [105]. Computational models corroborate this concept by suggesting that REM sleep is particularly favourable for associative learning [106].

Integrating the neural models of memory processing

Lewis and Durrant proposed a theory about schema-building (i.e., the information overlap to abstract (IOtA) theory) by combining the complementary learning systems model and the synaptic homeostasis hypothesis [107]. Specifically, these authors proposed that schemas emerge from an interaction between the reactivation of overlapping memories and synaptic downscaling during SWS. In the first step, overlapping reactivation of commonly shared elements may lead to greater strengthening of commonalities compared to more idiosyncratic aspects of a memory. In the second step, these strengthened memories may preferentially survive synaptic downscaling. In accordance with this theory and based on the evidence reviewed in this article, we believe that schema formation and schema integration take place primarily during SWS. In contrast, the disintegration of existing schemas might preferentially occur during REM sleep during which time associative processes are facilitated (Fig. 1).

However, the exact neural mechanisms and the translation of those mechanisms to the behavioural level remain largely enigmatic. It is possible that both SWS and REM sleep are related to various types of memory reorganisation and that there is no clear functional distinction between the two types of sleep. For example, no relationship has been observed between SWS and relational memory formation [18,40] and a correlation between the duration of REM sleep and rule-extraction in a probabilistic learning task has been reported [12]. These findings suggest that different neural activity patterns across the sleep period, rather than during a distinct sleep-stage, may be involved in distinct forms of memory reorganisation.

Modulation of memory reorganisation by emotions

Emotions critically modulate memories. To date, the majority of sleep studies have shown selective strengthening of emotional memories [108–110] and a bias toward information with a negative valence [111,112]. For example, Payne and colleagues [113] varied foreground and background objects in emotional pictures and found that the negative emotional objects in the foreground were strengthened relative to the background after sleep but not after an equal period of wakefulness. Additionally sleep seems to qualitatively reorganise emotional memory content. Indeed, Pace-Schott and colleagues demonstrated that fear extinction, when combined with sleep, is not specific to a particular stimulus but to a conditioned stimulus set. Extinction memories are generalised from extinguished conditioned stimuli to similarly conditioned but unextinguished stimuli only after sleep [114].

More specifically, REM-sleep might be particularly important for emotional memory processing in both animals [115,116] and humans [117–119]. Acetylcholine (which is up-regulated during REM-sleep) might have a particularly important role in the enhancement of emotional memory processing by, e.g., enhancing amygdala-dependent memory consolidation [120].

An important concept that pertains to the reorganisation of emotional memories during sleep is the ‘sleeping to remember and sleeping to forget hypothesis’ [120]. This hypothesis proposes that, during sleep, the connection between the informational and emotional components of a memory may be detached. This disconnection might result in a differential strengthening of the informational core of the experience in combination with a reduction in the affective tone and thus reorganise the original composition of the emotional and perceptual memory content. Of note, this concept is controversially discussed. Some studies did not find a reduction in the affective tone of emotional memories or even an increase in emotional reactivity after sleep [121–123].

The potential implications of sleep-related memory reorganisation for psychiatry and psychotherapy will be discussed in the final section.

Implications for psychiatry and psychotherapy

Mental disorders are among the major personal, societal and economic problems worldwide. In the current context, mental disorders can be conceptualised as both 1) a dysfunction of brain networks that results from an individual neurobiological disposition and 2) functional (health-promoting) and dysfunctional (disorder-promoting) memory traces that are acquired across the lifespan. The basic assumptions here are that sleep critically modifies memory and mental health and that sleep-related interventions have the potential to improve relevant health outcomes.

Sleep disruptions might impair memory and mental health

In line with this review, it is plausible to assume that sleep disruptions impair an adequate organisation of memories that may either facilitate the onset or worsen the course of a mental disorder. Direct evidence for this assumption is lacking, however, because it is not possible to disrupt sleep chronically to induce a mental disorder in healthy individuals. Thus, the notion is only supported by indirect evidence based on short-term sleep deprivation studies and observational longitudinal studies on the impact of sleep disruptions.

Sleep deprivation, as reviewed above, can significantly impair the reorganisation of newly encoded memories; however, the translation of these laboratory findings to clinically relevant settings (with prolonged sleep disruptions and mental health outcomes instead of short-term sleep deprivation and highly selected performance outcomes) is lacking.

In longitudinal studies, primary insomnia – a model of sleep disruptions in the absence of another disorder – has been shown to be associated with a decrease in the strengthening of declarative

[124] and motor memories [125,126]. In addition, primary insomnia has been identified as an independent risk factor for the *de novo* onset of a mental disorder, such as major depression [127]. Moreover, insomnia after an acute brain trauma predicts symptoms of depression and anxiety 12 mo post-injury [128]. Despite these findings, studies are lacking that characterise the impact of insomnia on the reorganisation of memories and its potential mediating effect for the development of a mental disorder.

Finally, sleep disruptions represent a prevalent (transdiagnostic) syndrome after the onset of a mental disorder [129]. Particularly, in posttraumatic stress disorder (PTSD), memory reorganisation is a central concept and main target for therapy. Chronic sleep disruptions after a trauma [130] might inhibit the functional integration of trauma-associated memories into pre-existing safety networks [29–31], which may increase the risk of developing PTSD [131–133]. In turn, short-term sleep loss directly after a trauma could serve an adaptive function by preventing the strengthening of traumatic experiences. Thus, one may speculate that immediate sleep loss after a trauma (reduced strengthening) and good sleep in a later phase (increased integration during therapy) might lead to beneficial outcomes.

Some support for the idea that sleep variables can modify the course of a mental disorder was illustrated in a study on depression. Cartwright and colleagues found that patients with major depression who did not dream of their ex-spouses following divorce exhibited worsened depression scores after five months [104]. This phenomenon was interpreted as impaired sleep-related memory integration as measured via dream-content; however, this interpretation is only relevant under the assumption that dreams are linked to the evolution of memories. In their review, Walker and Van der Helm further hypothesised that disturbances in the process of reducing emotional load while sleeping might result in the development of chronic anxiety [109].

Sleep-related interventions might improve memory and mental health

If memory processes during sleep are relevant to the onset and maintenance of mental disorders, then the targeted manipulation of sleep might provide inroads for the development of novel treatments. These interventions might be wide ranging, spanning from the simple timing of sleep to advanced neuromodulation techniques.

With regard to the timing of sleep, sleep deprivation selectively impairs the consolidation of fear in rats within 0–5 h, but not 5–10 h, following training [134]. If a similar phenomenon is present in humans, the existence of critical time windows may provide important opportunities; e.g., one may gain the opportunity to intentionally prevent the consolidation of traumatic experiences [109]. In turn, immediate sleep after psychotherapy could enhance the integration of new and functional memories and the transformation of dysfunctional thoughts. Thus, it may be possible to demonstrate that therapeutic interventions are more effective when therapeutic sessions are followed immediately by sleep, which may allow for more effective consolidation and integration of the therapeutic content [114,135]. Particularly, brief periods of daytime sleep immediately following exposure therapy led to significant decreases in fear in patients with spider phobias as measured via self-reports and catastrophic cognitions during approaching a live spider, and both of these measures correlated with stage 2 sleep [135]. The authors of that study attributed this augmentation of therapeutic effectiveness to the sleep-dependent strengthening of new memories established during the therapy. In PTSD therapy, the reactivation of consolidated traumatic memories is a common technique used to destabilise and modify the memory and then reintegrate a more health-promoting memory, which also could be intensified by periods of sleep immediately after a psychotherapy session.

Some authors have already begun to manipulate memory processing during sleep in both animals [136,137] and humans [138,139]. For example, animal studies have demonstrated that memory traces can be transformed or even erased by the administration of protein-synthesis inhibitors immediately before sleep [136]. Furthermore, modulation of sleep-specific brain activity patterns, such as the suppression of sharp-wave ripples by single pulse stimulation of the hippocampus during SWS in rats [137] and the non-invasive enhancement of slow oscillations in humans by transcranial direct current stimulation [140] or auditory closed-loop stimulation [141], has been shown to affect memory consolidation. Initial attempts to transfer these techniques to the treatment of patients with disorders such as schizophrenia have already been made. In patients with schizophrenia, declarative memory consolidation could be enhanced by the application of transcranial direct current stimulation during sleep [142]. In addition, the non-invasive approach of combining a visuo-spatial learning task with an odour during learning results in enhanced memory consolidation when participants are exposed to the conditioned stimulus while sleeping [143]. However, this effect is only observed when the odour stimulus is presented during SWS and not REM sleep. This mechanism of non-invasive memory modulation was recently replicated in a fear-extinction paradigm [144]. It would be of great interest to translate these findings into clinically relevant interventions and to elucidate further approaches for strengthening health-related and weakening disorder-related memories.

Finally, it should be mentioned that the concept of sleep-related memory and health can be broadened to neurological conditions. For instance, during rehabilitation after stroke or other brain lesions, reorganisation takes place at the neuronal level, leading to the acquisition of impaired functions by intact brain areas [145]. Given that sleep disruptions after stroke are highly prevalent [146], sleep-related interventions might improve the reorganisation of neural networks and clinically relevant outcomes.

Conclusion and future directions

The current review provides a critical overview of memory reorganisation during sleep. The studies reviewed suggest that sleep modulates the processes responsible for qualitative changes in memory. The most robust evidence is related to declarative memories, and fewer studies have dealt with qualitative changes in motor memory. Most studies have investigated memory changes on the behavioural level in humans. Due to difficulties in measuring the transformation of memory contents in animals, few animal studies on this topic exist.

On the neural level, the complementary learning systems theory, the synaptic homeostasis hypothesis and the spreading activation theory might complement each other. The current data suggest that relational memory formation and memory integration, rule and pattern extraction, and generalisation predominantly occur via the process of hippocampal–neocortical transfer during SWS. Associative processes might primarily occur during REM sleep. It remains unclear whether the formation of false memories results from gist extraction during SWS or from spreading activation during REM sleep.

The question of how the sleeping brain prioritises information is an important and largely open one. As qualitative changes in memory also take place without sleep, the question of whether there are sleep-specific neural processes that underlie the changes in memory that occur during sleep or if sleep merely fosters the process through reduced interference remains. Furthermore, the reorganisation of a memory trace from the hippocampus to the

neocortex does not necessarily entail changes in the memory on the behavioural level. Thus, studies that combine neurobiological and behavioural assessments are needed to further disentangle the relationship between neural reorganisation and qualitative changes in memory on the behavioural level.

The reorganisation of memory, particularly emotional memory, seems to be critical for mental health and well-being. Specifically, emotions seem to have an important modulating effect in the course of memory reorganisation which remains to be further characterised. Disentangling the relationships between sleep and qualitative changes in memory content and the reorganisation of memory on the neural level is important for our understanding of the development and maintenance of a variety of highly prevalent mental disorders, such as posttraumatic stress disorder and depression. Finally, disentangling these relationships might provide insights for the development of novel treatment strategies.

Disclosure of interest

Dieter Riemann has received speaker honoraria from AbbVie. Christoph Nissen has received speaker honoraria from Servier. None of the other authors has any conflict of interest to declare.

Practice points

- Sleep does not only strengthen memories but also reorganises them and results in qualitative changes in memory content on the behavioural level.
- Sleep-related memory reorganisation has been observed in the declarative and motor memory system.
- The formation of novel schemas and schema integration might preferentially depend on hippocampal–neocortical transfer during slow wave sleep. The disintegration of schemas and resulting associative thinking and creativity might be linked to spreading activation processes during REM sleep.
- The emotional value of information acts as an important modulator of memory reorganisation
- Clinically, disruptions of sleep are a transdiagnostic syndrome for many mental disorders and might result in deficits of memory reorganisation. Thus, sleep-related interventions may have the potential to modulate memory reorganisation and may improve the treatment of a number of mental disorders.

Research agenda

- How does the sleeping brain prioritise which information to strengthen, reorganise or forget?
- Are sleep-specific neural activity patterns needed for memory reorganisation? Or, alternatively, does sleep simply provide a window of reduced interference that allows for reorganisation?
- What is the relationship between qualitative changes in memory on the behavioural level and reorganisation on the neural level?
- What is the exact role sleep plays in the process of reorganising emotional memories?
- Does memory reorganisation during sleep influence the risk for the development or maintenance of mental disorders, such as posttraumatic stress disorder and depression? If so, can targeted interventions be developed to modulate memory reorganisation?

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